Epicardial propranolol administration for ventricular arrhythmias in dogs: matrix formulation and characterization

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The effect of propranolol on the prevention of ventricular tachycardia/fibrillation (VT/VF) due to acute coronary ischaemia was studied in dogs. A series of propranolol-polymer controlled release matrices in slab configuration using various polyurethanes and a polyurethane-silicone rubber copolymer were formulated and characterized. In general, drug release *in vitro* occurred with an initial burst phase followed by an exponentially declining delivery rate; the silicone rubber containing copolymer preparation had more sustained release properties than did pure polyurethane matrices. In the animal studies, dogs underwent 5-hourly 10 min complete occlusions of the left anterior descending coronary artery (LAD), followed by 50 min normal perfusion. During non-drug occlusions VT occurred at a frequency of 1.22 ± 0.12 episodes/min. A propranolol-polyurethane matrix (30% w/w, 28–42 mg) was placed on the ischaemic zone of the left ventricular epicardium immediately after the fifth occlusion. After an hour of drug delivery a sixth occlusion took place. The number of arrhythmia episodes both before and after drug were quantified and compared. The time to ventricular fibrillation (when present) and the mean blood pressure were also assessed. The drug patch delivered propranolol at a dose of 140 ± 45 μg/kg by the conclusion of the 1 h study period. Therapeutic drug levels were achieved in the peripheral blood samples (8.7–43.7 ng/ml) and were enhanced in coronary venous samples (360.9–556.2 ng/ml). Reduction of blood pressure and proarrhythmic events following epicardial controlled release propranolol administration were noted but were not statistically significant. Arrhythmia episodes before and after propranolol were not found to be significantly different (VT/min 1.02 ± 0.31 and 1.22 ± 0.12). The occlusion time until VF occurred was also not significantly different before *versus* after propranolol (t = 5.38 ± 0.86 and 5.28 ± 0.48 min). Therefore, despite attaining clinically therapeutic plasma levels, epicardial administration of propranolol was not found to be effective for the prevention of VT/VF due to acute ischaemia.

Keywords: Drug delivery, sustained release, β-blockers

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Ventricular arrhythmias are the most frequent cause of morbidity and mortality among patients with coronary heart disease[1–3]. Sustained ventricular tachycardia (VT) and ventricular fibrillation (VF) occurring after myocardial infarction are common and life threatening[1]. A variety of antiarrhythmic drugs are available for the management of ventricular arrhythmias[1, 3–5]. However, all of these agents have limitations. Undesirable characteristics such as narrow therapeutic indices[1, 4], cardiac and extracardiac side-effects[3–5], and proarrhythmic potential[6], limit the doses that can be administered systemically, thus complicating the treatment. When combination therapy is used, there is a potential for hazardous drug interactions[7].

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Since both the current pharmacological and the non-pharmacological treatments for ventricular arrhythmias are often ineffective and even dangerous, there is still need for an improved long-term therapeutic approach. A novel approach is the administration of the anti-arrhythmic drugs directly to the myocardium by implantable controlled release drug delivery systems[8–11].

Prior work has demonstrated that local controlled release administration of antiarrhythmic drugs using several different dog models was effective. For example, formulating a lidocaine–polyurethane controlled release matrix and implanting this drug delivery system on to the epicardium was found to be effective in converting ouabain-induced ventricular tachycardia in dogs to sinus rhythm[8]. Both lidocaine and procainamide polyurethane matrices were found effective for converting ventricular tachycardia induced by rapid ventricular pacing to sinus

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rhythm. Allowing those matrices to remain on the heart muscle for 4 h resulted in a ventricular tachycardia electrical induction threshold elevation that demonstrated a prolonged effect of those antiarrhythmic drugs[9, 10]. A verapamil-polyurethane matrix system was also found to be effective for reducing the number of VT/VF episodes due to a complete occlusion of the left anterior descending coronary artery (LAD) in dogs[11].

The doses of the antiarrhythmic drugs in all the above studies were significantly lower than conventional systemic doses. Coronary blood levels were found to be in the therapeutic range while peripheral blood levels, when detectable, were far below the therapeutic or the toxic range[8-11]. These results demonstrate the ability to treat ventricular arrhythmias by transmyocardial drug administration in experimental models. This route of administration has also been shown to optimize efficacy by enhancing local therapeutic concentrations, while minimizing general toxicity due to elevated plasma levels.

Controlled release matrices for the delivery of drugs locally to the heart were found to be effective in several other disease processes. For example, local delivery of gentamicin has made possible the prevention of bacterial endocarditis in a dog model[12]. Other studies have demonstrated the efficacy of both site-specific controlled release dexamethasone for the inhibition of fibrous tissue build-up near a pacing catheter[13], and diphosphonate matrix placement next to bioprosthetic heart valve leaflet implants for the prevention of calcification[14].

Controlled release of β-adrenergic antagonists has not been investigated for antiarrhythmia therapy. β-Adrenergic blockers have been classified as Type II antiarrhythmic drugs[15]. Currently β-adrenergic blockers are not first-line clinical agents for the treatment of any specific ventricular arrhythmia except in cases where the arrhythmia is associated with elevated catecholamine levels[4, 5].

However, the use of β-adrenergic blockers is well established in the treatment of atrial arrhythmias[4, 5, 16]. Furthermore, a number of clinical studies have demonstrated that administration of β-blockers prophylactically to patients after myocardial infarction can reduce cardiac mortality[1, 4, 5, 17], presumably due to preventing ventricular arrhythmias during subsequent ischaemic episodes. Other clinical studies have indicated that the β-adrenergic blockers can be useful in the treatment of benign or potentially fatal ventricular arrhythmias[18], treating patients with sustained ventricular tachyarrhythmias[19], and preventing sudden death[20-22].

A study that examined the effects of either timolol or propranolol on inducible sustained tachyarrhythmias in dogs found that both these β-blockers drugs were effective in abolishing inducible VT or VF in the dog with myocardial infarction[23]. Work by others using acute ischaemia models in dogs[24-26] has also demonstrated that systemic administration of propranolol reduced the incidence of ventricular arrhythmias. Thus, both the clinical and the animal studies of the β-adrenergic blockers have established their potential usefulness in treating ventricular arrhythmias.

In the present study propranolol, a non-specific moderately potent β-blocker, served as a model drug for studying the effect of β-blockers on the ischaemic heart, when administered locally, directly to the myocardium via a controlled release matrix. The objectives of this study were:

1. To formulate and characterize the *in vitro* release profile of propranolol from various polymeric matrix preparations and to choose a suitable matrix for *in vivo* studies.
2. To study the pharmacological effects of the propranolol matrix *in vivo* for inhibition of ventricular arrhythmias in an ischaemic model in dogs.
3. To examine and compare coronary and peripheral propranolol blood levels during controlled release epicardial drug delivery.

EXPERIMENTAL

Materials

Propranolol hydrochloride and quinidine (HPLC internal standard) were obtained from Aldrich Chemical Corp. (Milwaukee, WI, USA). Two proprietary polyether (polytetramethylene glycol) polyurethanes MPU-5 (Matrix Media Inc., Wheat Ridge, CO, USA) and Biomer (Ethicon, Somerville, NJ, USA) were used, as 25% and 30% in dimethylacetamide. A proprietary polyurethane-silicone rubber copolymer 6605-41 (Dow Corning Corp., Midland, MI, USA) was also used for preparing drug matrices. HPLC grade acetonitrile and methanol were obtained from Mallinckrodt Inc. (Paris, KY, USA). HPLC grade ether and phosphoric acid (85%) were obtained from Fisher Scientific (Pittsburgh, PA, USA). Dimethyacetamide (DMA) and ascorbic acid were purchased from Sigma (St Louis, MO, USA).

Apparatus

Electrocardiograms were continuously recorded on a Hewlett-Packard 3698A Instrumentation Recorder (Andover, MA, USA), displayed on AST premium 286 computer (AST Research Inc., Irvin, CA, USA), using a Codas analog to digital conversion board plus software (Data Q Instruments Inc., Akron, OH, USA). Periodically physiological readings were also produced using a pressurized ink system (Hewlett-Packard, Model PDR-HP). A programmable stimulator (Grass Instruments, Model S88, Quincy, MA, USA) coupled to an optically isolated constant current source (Bloom Associated Ltd, Reading, PA, USA) were used for pacing. Propranolol assays were carried out with a high-performance liquid chromatograph (Waters 501 HPLC Pump, Waters Inc. Milford, MA, USA) with a Waters 680 Automatic Gradient Controller which was equipped with a prepacked C18 precolumn (Waters Inc.) and an Altex Ultraspheric-ODS, 25 cm × 4.6 mm column (Beckman Inc., San Ramon, CA, USA). The detection of the drug was carried out with a Waters 470 scanning fluorescent detector and chromatograms were received on a Waters 740 Data Module (Waters Inc.).

METHODS

Matrix formulation and *in vitro* release studies

Propranolol hydrochloride matrices were prepared by dissolving the drug in DMA and adding the polymer of

interest already dissolved in DMA. The mixture was then poured into Teflon® coated Petri dishes (10 cm diameter) and were dried in a vacuum oven at 50°C for 48 h. Propranolol polymer films were cut into 1 × 1 cm (200 μm thick) squares for *in vitro* release, in triplicate, using 0.05 mM phosphate buffer under perfect sink conditions (20 ml volumes at pH 7.4, 37°C, 45 rev min^{-1} changed daily). Propranolol release was quantitated by UV absorbance (λ_{max} = 289 nm). The calibration curve was found to be linear in the range that was used (5–100 μl/ml).

Stability test

To assess the stability of propranolol during the *in vitro* release study and storage periods, six solutions in a concentration range 5–100 ng/ml were prepared, divided into groups and stored at 4 and 37°C. The UV readings of the freshly prepared solutions were compared with the UV readings of the same solutions after 1 and 7 d in the storage conditions.

Dog model of ischaemic ventricular tachycardia (VT) and ventricular fibrillation (VF)

Six male mongrel dogs (24–35 kg) underwent a left thoracotomy and pericardiotomy under pentobarbital anaesthesia. A bipolar platinum electrode was placed on the left atrial appendage and pacing was carried out during each study at 180 beats/min using twice the diastolic capture threshold current. Surface electrodes and unipolar epicardial electrodes (on ischaemic and non-ischaemic zones of the left ventricle) were used for electrocardiogram recordings. The blood pressure and the pacing electrode signal were also recorded. Each animal was subjected to 5-hourly 10 min complete occlusions of the LAD followed by 50 min of normal perfusion. Five replicate occlusions were carried out to assure the reproducibility of arrhythmias in each dog before therapy. This dog model is a modification of the method described by Elharrar *et al.*[27]. In the current model, the hearts underwent a 10 min complete occlusion, as opposed to 6 min used by Elharrar *et al.*[27]. To normalize the data, the numbers of premature beats (PM), doublets (DB) and ventricular tachycardia (VT) episodes were calculated per minute. One of the common consequences of the repeated occlusions was ventricular fibrillation (VF) either during the occlusion or with reflow. In the event of fibrillation during an occlusion, the occluder was released and the dog resuscitated with a DC defibrillator.

Arrhythmia episodes were counted during each occlusion period and during the intervening periods after the fourth and fifth occlusions. Two consecutive premature beats were defined as a doublet while three or more were defined as ventricular tachycardia. Immediately after the fifth occlusion a propranolol patch was put on the LAD ischaemic zone. After the patch was in place for an hour the last 10 min occlusion was carried out. Blood samples were collected from the femoral and regional coronary veins every 10 min during the drug study period. Before storage at −20°C ascorbic acid (to a 5 mg/ml concentration) was added to the separated plasma to prevent propranolol oxidation[28].

Blood samples analysis

Peripheral and coronary venous propranolol levels were measured using a modification of an HPLC method that was described by Abdel-Hamid[28]. To a 1 ml aliquot of thawed peripheral plasma samples 100 μl of internal standard solution (Quinidine, 10 μg/ml), 1 ml of a sodium hydroxide solution (1.0 M), 1 ml of water and 5 ml ether were added. After vortexing for 30 s and centrifuging for 10 min at 1800 rev min^{-1} the aqueous layer was frozen over an isopropranol–dry ice bath and the ethereal phase was separated. Then 200 μl 0.1% phosphoric acid containing 5 mg/ml ascorbic acid were added to the ethereal phase, mixed, centrifuged and frozen. After discarding the ethereal layer the frozen pellets were thawed and 50 μl were injected into the HPLC. From the thawed coronary plasma only 0.5 ml aliquots were taken and NaOH (0.25 ml) and water (0.25 ml) were added. A calibration curve was prepared in 1 ml blank dog plasma containing 5 mg/ml ascorbic acid and was found to be linear in the range that was checked (10–300 ng/ml).

Residual matrix drug detection

Retrieved propranolol hydrochloride matrices in MPU-5 were extracted with methanol in a Soxhlet apparatus (Fisher Scientific). The extracts were analysed by HPLC (see later) and the net *in vivo* release was calculated.

HPLC conditions

An isocratic separation was achieved as follows: the mobile phase was prepared by combining 56 ml phosphoric acid solution (0.02 M, pH 4) with 28 ml of acetonitrile and 16 ml of methanol[28]. The flow rate was 1 ml/min. A combination of 212 nm excitation filter and 340 nm emission filter were used for fluorescence detection. These conditions were used for quantitation of both the residual matrix propranolol after application and the blood samples.

RESULTS

In vitro release

Propranolol was previously found[29] to be unstable at alkaline pH. To be certain that propranolol was stable during the release study at 37°C and during storage at 4°C, the slopes of the calibration curves were compared after storage at each temperature. The slope of the 'freshly prepared' calibration curve was not found to be significantly different from the slopes of the calibration curves of the solutions stored at 37 and 4°C after 1 d ($y = 1.86 \times 10^{-2}x$, $1.87 \times 10^{-2}x$, $1.86 \times 10^{-2}x$) or 7 d ($y = 1.86 \times 10^{-2}x$, $2.03 \times 10^{-2}x$, $1.89 \times 10^{-2}x$).

The release rates of propranolol from four different formulations were quantified and compared up to 10 d (*Figure 1*). While the polyurethane preparations were releasing most of the drug during the first day, the copolymer matrix released only about 15% of its content over 10 d. When comparing the release up to 60 min, which was the duration of the *in vivo* release up to the drug test occlusion it was found that the matrix that contained 30% propranolol hydrochloride in MPU-5 released 66.5 ± 4.4% (mean±SD). However, the 20%

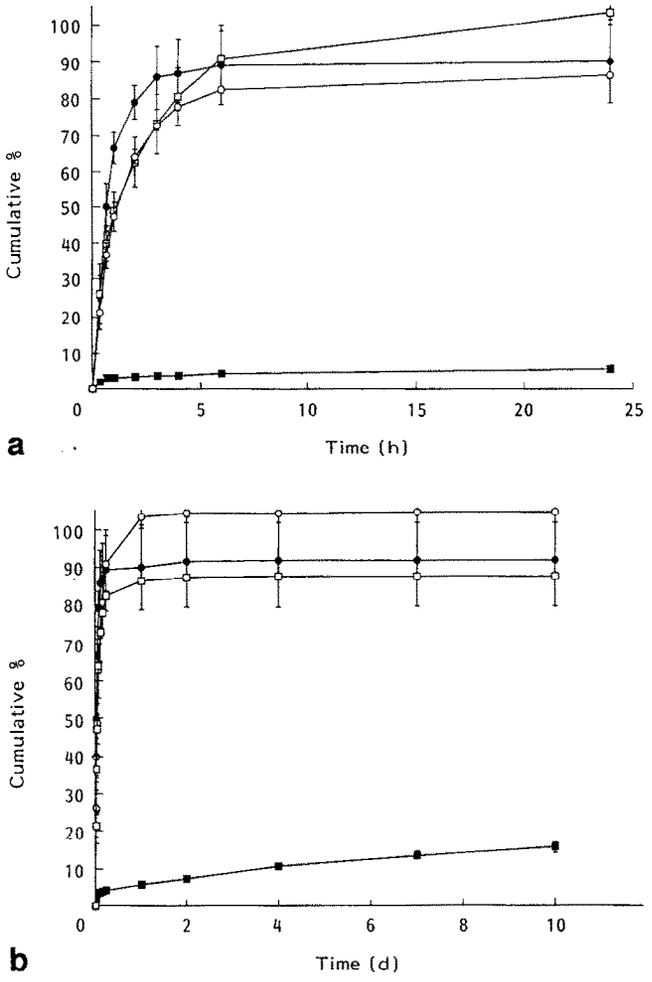

Figure 1 Propranolol *in vitro* release as cumulative percentage (37°C, pH 7.4) from 30% MPU-5 (□), 20% MPU-5 (●), 20% polyurethane-silicone rubber copolymer (■) and 20% Biomer (○). **a**, 24 h, **b**, 10 d.

propranolol loaded matrices in MPU-5, Biomer and the copolymer released 47.2 ± 3.9%, 48.7 ± 5.5% and 3.25 ± 0.3% respectively. Since the amount of drug released from the 30% MPU-5 matrices was significantly greater than the amount released from the 20% preparations in MPU-5 and Biomer ($t = 8.36$, $P = 0.001$ and $t = 6.81$, $P = 0.002$ respectively) the matrix that contained 30% propranolol in MPU-5 was used for the *in vivo* studies.

Arrhythmia experiments

Dose

Following *in vivo* release (70 min) in the dogs, the drug matrices were extracted for residual propranolol content. It was found that 140 ± 45 μg/kg of propranolol were delivered.

Occlusion experiments

Analyses of the frequency of the different types of ventricular arrhythmias, premature (PM), doublet (DB) and ventricular tachycardia (VT) beats during the occlusion periods and during the intervals following the fourth and fifth occlusions demonstrated that frequencies of each type of ventricular arrhythmia per minute during acute ischaemia were not significantly different with or without propranolol. VT frequencies (episodes per minute, mean ± standard error) for occlusions 1 through 5 were 1.40 ± 0.38, 1.09 ± 0.35, 0.80 ± 0.32, 1.18 ± 0.60 and 1.34 ± 0.49 respectively. Following 1 h propranolol epicardial administration VT frequency was 1.02 ± 0.31. The results are summarized in *Table 1* and *Figure 2*. To examine the proarrhythmic effect of propranolol, the interval following the fourth occlusion, before the drug matrix was sewn on, and the interval after the fifth occlusion, following the matrix placement, were compared. Although the frequency of PM beats, DB and VT per min was greater during the hour after propranolol was administered to the heart compared to the control the differences were not significant statistically ($P > 0.5$, Student's t test). Propranolol also tended to reduce the mean blood pressure; the reduction was also not significant statistically ($P > 0.5$) compared to control. In addition, propranolol did not influence the onset of ventricular fibrillation.

Peripheral versus *coronary blood levels following epicardial propranolol*

Peripheral propranolol levels ranged from 8.7 to 43.7 ng/ml, while simultaneous coronary blood levels were significantly elevated ($P < 0.001$) compared with peripheral levels, and ranged from 360.6 to 556.2 ng/ml (*Figure 3*), emphasizing the enhanced regional nature of epicardial controlled release therapy.

DISCUSSION

In the present study the *in vitro* release rate was found to be influenced by the nature of the polymer in which the drug was compounded. The release rate from MPU-5, the most hydrophilic polymer used in our investigation, was significantly higher than the release rate from the other polyurethane studied, Biomer, which is relatively less hydrophilic than MPU-5. Furthermore the release rate of propranolol from the copolymer 6605-41 which was the least hydrophilic polymer investigated, since it is a polyurethane-silicone rubber, was more sustained than noted with MPU-5 or Biomer. The same trend was previously found[30] for the release of $FeCl_3$ and $Al(NO_3)_3$ from Biomer and the copolymer 6605-41. The ability of these various polymer matrices to deliver a range of antiarrhythmic drug doses over prolonged periods of time is of particular importance; for an acute arrhythmia a higher dose for a short period of time might be needed, while for maintenance of an inhibitory drug level for chronic arrhythmia therapy a lower dose over a long period of time might be needed.

The propranolol coronary blood levels were also shown to be up to 50 times greater than the peripheral levels. This result emphasizes the propensity for epicardial controlled release to achieve regionally high drug levels while minimizing the magnitude of systemic blood levels. The same phenomenon was demonstrated when either lidocaine[9] or procainamide[10] were administered to the heart by controlled release matrices. Plasma propranolol levels of up to 1000 ng/ml may be required to control resistant ventricular arrhythmias based on clinical results[4]. However, only 25% of the usual

Table 1 Comparison of frequencies of arrhythmic episodes, time to VF and blood pressure with and without propranolol*

	Control (1st to 5th occlusions combined)	Propranolol	4th reflow	5th reflow
Occlusions (*n*)	30	6	6	6
PM/min	2.5 ± 0.68*	2.64 ± 0.69	0.10 ± 0.06	0.46 ± 0.27
DB/min	0.75 ± 0.31	0.69 ± 0.14	0.03 ± 0.03	0.26 ± 0.14
VT/min	1.22 ± 0.12	1.02 ± 0.31	0.02 ± 0.01	0.07 ± 0.05
Time to VF (min)	5.28 ± 0.48	5.38 ± 0.86	-	-
Mean BP (mmHg)	153.6 ± 6.5	131.3 ± 16.5	-	-

Data are mean ± sem.
PM, premature; DB, doublet; VT, ventricular tachycardia; VF, ventricular fibrillation; BP, blood pressure.

antiarrhythmic dose, 140 μg/kg, was needed to achieve a nearly maximal therapeutic level in the coronary blood in the present study. Also, according to our results, when propranolol was given locally the peripheral drug levels were within the low end of the therapeutic range for treating angina and hypertension based on clinical studies[4].

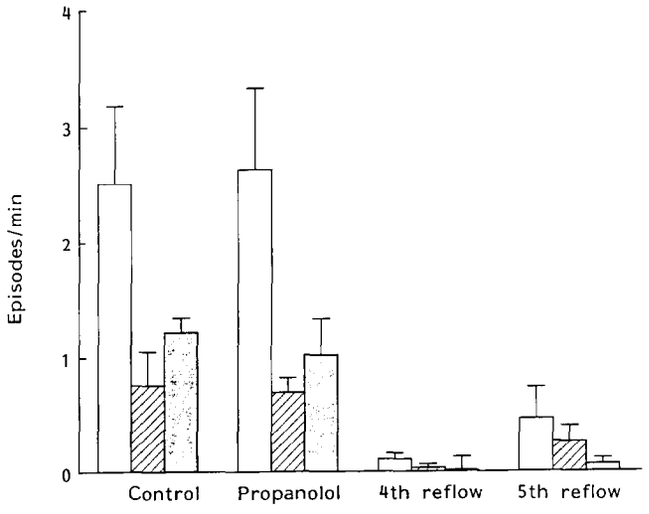

Figure 2 Frequency of arrhythmia episodes with and without propranolol during occlusion and reflow. Isolated premature beats (□), doublets (▨), ventricular tachycardia (■).

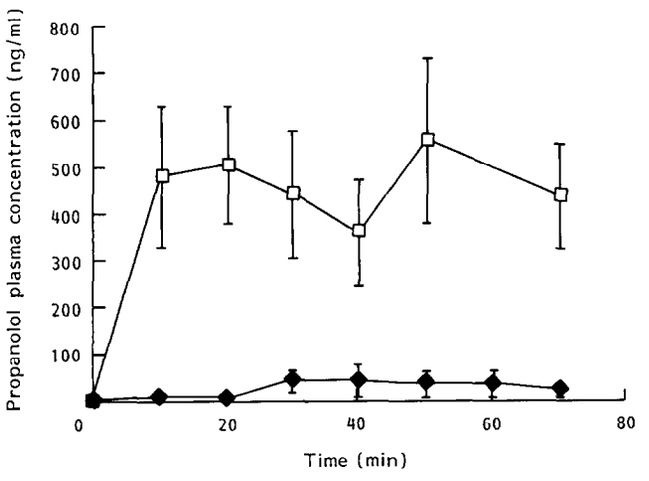

Figure 3 Propranolol plasma levels (ng/ml, means ± standard errors). Coronary (□), peripheral (●).

Although propranolol epicardial administration resulted in significantly higher blood levels in the heart compared with the peripheral blood, no significant antiarrhythmic effect was demonstrated. Furthermore, peripheral plasma-propranolol levels were also in the therapeutic range relative to clinical data concerning both arrhythmia therapy and hypertensions[20-22, 31]. Prior animal and clinical studies have also demonstrated that systemic propranolol reduces the occurrence of ventricular arrhythmias due to myocardial ischaemia[20-22, 24-26] or infarction[1, 4, 5, 17, 20]. Furthermore, systemic administration of propranolol by others has been effective in dog models of ischaemia comparable to ours[24-26] and also infarction-related arrhythmias using net total dosages comparable to those used in the present study[20]. These prior studies cannot be viewed as providing systemic drug administration of relevance for the present experiments. Thus, additional drug protocols in the present series of studies could have compared an array of systemic dosages of propranolol to the epicardial results. However, the lack of any antiarrhythmia activity with epicardial controlled release compared to non-drug coronary occlusions, despite near maximal coronary venous drug concentrations, and systemic hypotension obviates the usefulness of further studies along these lines. Furthermore, a relevant systemic dose for comparisons with the epicardial studies might have involved giving the same dose administered by the matrix intravenously over 1 h, or administering an appropriate intravenous dose based on pharmacokinetic parameters to achieve a systemic or coronary propranolol level identical to that achieved with epicardial administration. Other treatment groups could also have considered regional intracoronary injection of propranolol or coronary venous retro-perfusion, again to obtain coronary venous plasma levels identical to those achieved with a matrix. These other administration variations were beyond the scope of this study but may be worth further consideration.

In addition the present results suggest that while systemic β-blockade may be effective for ventricular arrhythmias this is likely be due to central effects rather than directly influencing cardiac β-adrenergic activity. Alternatively, D-propranolol for suppression of ventricular arrhythmias in man has recently been shown to be as effective as the racemic preparation[32], thereby demonstrating that propranolol's efficacy for ventricular arrhythmias may not be entirely related to its β-blocking.

Table 2 Comparisons of epicardial polymeric (polyurethane) controlled release therapy: results of acute ischaemia-ventricular tachycardia (VT) studies in dogs[a]

Drug	Class[b]	Mechanisms	Loading	Dose (mg/kg/2 h)	*n*	VT (per/min)
Lidocaine	I	Na channel blockade	28%	0.23	5	0.6 ± 0.2
Propranolol	II	β-blocker	30%	0.14	6	1.22 ± 0.12
D-Sotalol	III	Delayed repolarization	30%	0.20	9	0.46 ± 0.11
Verapamil	IV	Calcium channel blocker	30%	0.30	11	0.10 ± 0.03
No therapy	-	-	-	-	9	1.10 ± 0.30

[a]Modified from Levy *et al.*, in *Cosmetic and Pharmaceutical Application of Polymers*, Plenum, NY, USA, 1991, pp 231-238.
[b]Vaughan Williams classification[15].

Therefore, propranolol's failure to affect ventricular arrhythmias via epicardial administration may be due to complex and incompletely understood factors.

The tendency observed in the present studies for epicardial propranolol to reduce blood pressure and to intensify arrhythmias during non-ischaemic periods was not found to be statistically significant. Nevertheless, this possible β-adrenergic antagonist effect might be better investigated in further experiments planned with sotalol. Sotalol, a relatively new antiarrhythmic drug, has two active stereoisomers. The L-isomer has β-blocker activity, while D-sotalol is classified as a class III antiarrhythmic drug[33]. Thus, experiments with each of the isomers and with the racemic mixture might be most useful for further studying the importance of β-blockers for antiarrhythmia therapy.

Despite the lack of effectiveness of epicardial controlled release propranolol in this ischaemic ventricular arrhythmia model system, virtually all the other classes of antiarrhythmic agents have been shown to be effective for decreasing the occurrence ischaemic arrhythmias in this dog model when administered by epicardial controlled release matrices (*Table 2*)[34]. Thus, further research investigating myocardial β-blockade via epicardial controlled release may not prove to be as fruitful as other mechanistic strategies.

CONCLUSIONS

Propranolol, serving as a model β-adrenergic antagonist, was successfully delivered from a polyurethane matrix placed on the left ventricular epicardium in dogs. Although potentially therapeutic blood levels were achieved both in the heart and in the periphery, epicardial propranolol, while causing mild hypotension, failed to prevent ventricular arrhythmias due to acute ischaemia. Thus it was not found to be useful as a treatment for ventricular arrhythmias due to acute ischaemia in a dog model system.

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